

Original article

Herbal supplements and skin testing: the lack of effect of commonly used herbal supplements on histamine skin prick testing

Background: The use of herbal supplements is common, yet little is known about their pharmacologic properties. The purpose of this study was to assess the effects of 23 commonly used herbal supplements on histamine skin prick testing (SPT).

Methods: Fifteen healthy volunteers participated in a double-blind, placebo-controlled, single-dose, crossover study. Wheal and flare responses to SPT with histamine phosphate (1 mg/ml) were measured before and 4 h after administration of each of the 23 popular herbal supplements, fexofenadine (60 mg) and placebo. Wheal and flare areas were recorded with tracings performed 10 min after the prick test and measured with a PC-digitizer using stereometric software.

Results: Fexofenadine significantly suppressed the wheal ($P < 0.001$) and flare ($P = 0.02$) areas compared with placebo. None of the herbal supplements caused significant suppression of the wheal and flare areas compared with placebo ($P > 0.10$).

Conclusion: When taken in single-doses, the popular herbal supplements tested did not significantly affect the histamine skin response. Therefore, it seems unnecessary for clinicians to ask patients to discontinue these herbal supplements prior to allergy skin testing.

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The use of alternative medicine is on the rise in the United States (1–3). As of 1997, more patients sought care from alternative medicine practitioners than from primary care physicians (1). A large component of this alternative medicine is in the form of herbal supplements (1). Approximately 20% of individuals taking prescription medications are concurrently using herbs, high-dose vitamins, or both (1). While the use of herbal supplements is common, little is known about their pharmacological properties (4, 5). Many herbs are presumed to possess diverse properties such as anti-inflammatory or anti-allergy effects (3, 6–11) yet their effect on the histamine skin response is unknown. Patients who are undergoing allergy skin testing are routinely told to avoid medications that exert anti-histaminic properties, which could alter the test outcome and lead to false negative results (12). Presently, many clinicians do not ask patients to stop herbal supplements prior to allergy skin testing. Given the widespread use of herbal supplements, it would be important to know the effects of herbal supplements on allergy skin testing.

The purpose of this study was to determine the effects of 23 popular herbal supplements (13–17) on histamine skin prick testing (SPT), and to compare these effects with an H1 antagonist, as well as to placebo.

Methods

The protocol for this randomized, double-blind, single-dose, crossover study was approved by the Wilford Hall USAF Medical Center Investigational Review Board. Each participant gave written informed consent prior to initiation into the study. Fifteen healthy subjects were recruited based on being in a state of good health, of being at least 18 years of age, and not requiring regular administration of H1 or H2 antagonists, tricyclic antidepressants, nonsteroidal anti-inflammatory agents, herbal supplements or high-dose vitamins. Subjects were excluded if they were pregnant or breast feeding, had any acute illness, current smokers, had an inadequate response to a baseline histamine SPT (< 3 mm in diameter), demonstrated dermatographism, or had a skin disorder precluding the placement and reading of a histamine skin test. Nonpregnancy status was determined with a qualitative urinary pregnancy test.

Herbal supplements tested included aloe 25 mg, astragalus 250 mg, bilberry 80 mg, cascara sagrada 500 mg, cat's claw 500 mg, cayenne 500 mg, devil's claw 150 mg, echinacea 300 mg, evening primrose 500 mg, feverfew 500 mg, garlic 810 mg, ginger 500 mg, ginkgo 50 mg, ginseng 500 mg, goldenseal 500 mg, gotu kola 500 mg, grape seed extract 50 mg, green tea 150 mg, licorice 500 mg, milk thistle 200 mg, saw palmetto 500 mg, St John's wort 300 mg and valerian 500 mg (all herbal supplements were products of General Nutrition Corporation, Pittsburgh, PA, USA). The dosages chosen represented an average dose as recommended by the manufacturer. Fexofenadine (60 mg) and placebo were used as positive and negative controls, respectively. Each blinded supplement or medication was administered in a single oral dose to each

Table 1. Effects of herbal supplements on the histamine skin response. Wheal suppression (WS) and flare suppression (FS) are shown as a percent decrease in wheal and flare areas compared with placebo. Negative suppression refers to augmentation of the areas

Herbal supplement	WS		FS	
	Percentage	<i>P</i>	Percentage	<i>P</i>
Fexofenadine	75	<0.001	89	0.02
Licorice	21	0.196	36	0.378
Green tea	19	0.339	2	0.891
Saw palmetto	19	0.122	-38	0.699
St John's wort	15	0.256	-95	0.165
Feverfew	15	0.344	-3	0.878
Devil's claw	9	0.901	-21	0.832
Ginger	8	0.693	-43	0.104
Aloe	6	0.652	1	0.757
Bilberry	4	0.575	-19	0.888
Echinacea	4	0.757	8	0.777
Cascara sagrada	2	0.972	-110	0.124
Valerian	1	0.872	18	0.374
Evening primrose	1	0.816	8	0.674
Golden seal	1	0.833	17	0.587
Garlic	1	0.665	-4	0.889
Cat's claw	-4	0.891	2	0.880
Cayenne	-5	0.719	34	0.144
Grape seed extract	-6	0.774	-45	0.538
Gotu kola	-6	0.807	-19	0.779
Ginkgo	-6	0.801	-40	0.619
Ginseng	-10	0.673	33	0.356
Astragalus	-15	0.305	-121	0.202
Milk thistle	-24	0.335	-13	0.885

subject with an 8-oz glass of water. Subjects were advised to go about their usual morning routine including routine intake of food and beverages during this time.

Subjects presented to the allergy clinic at 8 AM for a baseline histamine skin test prior to each supplement and again 4 h after (18) each supplement. A modified prick-and-wipe method was performed using a surgical needle (Anchor Products, Addison, IL, USA) and histamine phosphate (Center Laboratories, Port Washington, NY, USA), 1 mg/ml, along with normal saline (0.9% NaCl) control, on the volar surface of the left forearm. Wheal and flare circumferences were traced for 10 min on transparent paper (18, 19). Wheal and flare areas were measured with a PC-digitizer using stereometric software (18, 19). All histamine-induced wheal and flare areas were analyzed as percent suppression of the predose value. Percent suppression of the wheal and flare was calculated as follows (18, 19): $[\text{area}_{(\text{predose})} - \text{area}_{(\text{postdose})}] / \text{area}_{(\text{predose})} \times 100$.

References

1. EISENBERG DM, DAVIS RB, ETTNER SL, APPEL, S, WILKEY S, VAN ROMPAY M, KESSLER, RC. Trends in alternative medicine use in the United States, 1990–1997: results of a follow-up national survey. *JAMA* 1998;**280**:1569–1575.
2. EISENBERG DM, KESSLER RC, FOSTER C, NORLOCK FE, CALKINS DR, DELBANCO TL. Unconventional medicine in the United States – prevalence, costs, and patterns of use. *N Engl J Med* 1993;**328**:246–252.
3. BIELORY L. Complementary medicine for the allergist. *Allergy and Asthma Proc* 2001;**22**:33–37.
4. BAUER BA. Herbal therapy: what a clinician needs to know to counsel patients effectively. *Mayo Clin Proc* 2000;**75**:835–841.

Each subject underwent the same process for each of the 23 herbal supplements and control medications as listed above, with a minimum washout period of 72 h between dosages. In addition, patients were asked about side-effects at the time of the second skin test for each.

Statistical analysis was accomplished with the assistance of a statistician. A power analysis revealed that a sample size of 13 would achieve a power of 95% to detect a 30% suppression of wheal and flare areas. A two-tailed *t*-test was used for all comparisons, with significance defined as $P < 0.05$.

Results

All 15 subjects completed the study. Each herbal supplement was taken by at least 13 participants, and all 15 subjects took fexofenadine and placebo.

Fexofenadine significantly suppressed the mean wheal (75%; $P < 0.001$) and flare (89%; $P = 0.02$) areas, compared with placebo. None of the herbal supplements caused significant suppression of the wheal and flare areas compared with placebo ($P > 0.10$; see Table 1).

Adverse side effects caused by the supplements were minor and limited to gastrointestinal symptoms such as dyspepsia, nausea and diarrhea. No subjects dropped out of the study because of side-effects.

Discussion

Herbal supplements are commonly used over-the-counter products often taken in addition to, or in place of, prescription medications (1). Despite their widespread use, little is known about their pharmacologic properties (4, 5), including whether popular herbal supplements suppress the histamine skin response. We have shown that, when taken as a single-dose, the popular herbal supplements tested demonstrated no statistically significant effects on wheal or flare areas.

Further studies need to be undertaken with higher and long-term dosages of herbal supplements, and herbal supplements taken in combination to determine if these factors would result in significant suppression of the histamine skin response. As a result of this study, there appears to be no need for clinicians to ask patients to discontinue the use of these popular herbal supplements prior to allergy skin testing.

5. BERNSTEIN DI, BERNSTEIN CK, DENG C, et al. Evaluation of the clinical efficacy and safety of grapeseed extract in the treatment of fall seasonal allergic rhinitis: a pilot study. *Ann Allergy Asthma Immunol* 2002;**88**:272–278.
6. ZIMENT I, TASHKIN DP. Alternative medicine for allergy and asthma. *J Allergy Clin Immunol* 2000;**106**: 603–14.
7. HUNTLEY A, ERNST E. Herbal medicines for asthma: a systematic review. *Thorax* 2000;**55**:925–929.
8. GRAHAM DM, BLAISS MS. Complementary/alternative medicine in the treatment of asthma. *Ann Allergy Asthma Immunol* 2000;**85**:438–449.
9. FRIERI M. Herbal therapies: what allergist-immunologists should know regarding patient use of complementary and alternative medicine. *Allergy and Asthma Proc* 2001;**22**:209–215.
10. HU G, WALLS RS, BASS D, et al. The Chinese herbal formulation biminne in the management of perennial allergic rhinitis: a randomized, double-blind, placebo-controlled, 12-Week clinical trial. *Ann Allergy Asthma Immunol* 2002;**88**:478–487.
11. SCHAPOWAL A. Randomized controlled trial of Butterbur and Cetirizine for treating seasonal allergic rhinitis. *BMJ* 2002;**324**:1–4.
12. BERNSTEIN IL, STORMS WW. Practice parameters for allergy diagnostic testing. *Ann Allergy Asthma Immunol* 1995;**75**:553–625.
13. NELSON L, PERRONE J. Herbal and alternative medicine. *Emerg Med Clin North Am* 2000;**18**:709–722.
14. MILLER LG. Herbal medicinals. *Arch Intern Med* 1998;**158**:2200–2211.
15. WINSLOW LC, KROLL DJ. Herbs as medicines. *Arch Intern Med* 1998;**158**:2192–2199.
16. American Botanical Council. Available at: <http://www.herbalgram.org/>. Accessed August 13, 2002.
17. CALDERON L. Current concepts in nutrition: top herbal sales in U.S. Available at: <http://web.calstatela.edu/faculty/lcalder/411/tsld115.htm>. Accessed August 13, 2002.
18. SIMONS FER, McMILLAN JL, SIMONS KJ. A double-blind, single-dose, cross-over comparison of Cetirizine, Terfenadine, Loratadine, Astemizole, and Chlorpheniramine versus placebo: suppressive effects on histamine-induced wheals and flares during 24 hours in normal subjects. *J Allergy Clin Immunol* 1990;**86**:540–547.
19. SIMONS FER, SIMONS KJ. Peripheral H1-blockade effect of Fexofenadine. *Ann Allergy Asthma Immunol* 1997;**79**:530–532.